"and pharmaceutically" wherein the Examiner requests a correction. Applicants amend the claim accordingly.

Claims 3, 4, 7, 8, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. In particular, the Examiner asserts that the phrase "acceptable salt" is confusing and suggests amending the phrase to be "acceptable salt thereof." Applicants amend the claims accordingly.

Claims 13 and 14 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. In particular, use claims are not considered a permitted class of invention wherein the Examiner suggests recitation of a method or process that includes at least one step. Applicants cancel without prejudice Claim 13 and amend Claim 14 accordingly.

Claims1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by *Baichwal et al.* (US Pat. No. 5,399,359).

Claims 7-14 are rejected under 35 U.S.C. 102(b) as being anticipated by *Aberg et al.* (US Pat. No. 5,532,278).

Claims 3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being obvious over *Baichwal et al.*

Claims 7-14 are further rejected under 35 U.S.C. 103(a) as being obvious over *Baichwal et al.* in view of *Aberg*.

Claim Objections

Claim 5 is objected to on the grounds that "an pharmaceutically" should read "and pharmaceutically" wherein the Examiner requests a correction.

Applicants amend this claim to such that the phrase reads "and a pharmaceutically."

Accordingly, this objection should be withdrawn and the claim is in condition for approval.

Claim Rejections – 35 USC § 112, second paragraph

Claims 3, 4, 7, 8, 10 and 11 are rejected under 35 U.S.C. § 112, second paragraph, as being confusing with respect to the phrase "acceptable salt." The Examiner graciously suggests amending the phrase to be "acceptable salt thereof" to eliminate any potential for confusion.

Applicants amend the noted claims as suggested by the Examiner.

Accordingly, the rejection should be withdrawn and the claims are in position for allowance.

Claim Rejections – 35 U.S.C. § 101

Claims 13 and 14 are rejected for claiming non-statutory subject matter. In particular, the Examiner asserts that use claims are not considered a permitted class of invention.

Applicants cancel without prejudice Claim 13 and amend Claim 14 to claim a method of manufacture.

Accordingly, no non-statutory claims remain and it is submitted that Claim 14 is now in condition for allowance.

Claim Rejections – 35 U.S.C. § 102(b) anticipation

Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by *Baichwal et al.* (US Pat. No. 5,399,359). In particular, the Examiner asserts that *Baichwal* discloses a sustained release formulation comprising from about 5 mg to about 20 mg oxybutynin and its pharmaceutically acceptable salts thereof.

This rejection is respectfully traversed because Applicants amended claims distinctly claim a unique dosage form for increasing the therapeutic index of oxybutynin.

Applicants' invention unexpectedly decreases the oxybutynin metabolism. Applicants page 30 and 33. As a result, there is a higher bioavailability of oxybutynin from Applicants' invention compared to immediate release oxybutynin. Applicants page 33. The prior art sustained release matrix formulations on the other hand were found to release more than 50% of their active ingredient within the first four hours such that the bioavialability is reduced compared to Applicants' invention. Applicants page 32.

Additionally, it was found that the prior art matrix dosage form was significantly affected by meals. Applicants page 32. As such, the prior art loses its sustained release property when taken with meals. Applicants page 32. However, Applicants

claimed invention was found to have sustained blood plasma concentrations, unaffected by meals. Applicants page 33.

These factors demonstrate that Applicants claimed invention uniquely increases the therapeutic index of oxybutynin over immediate release dosage forms and more importantly, over the prior art matrix sustained release dosage forms. Applicants page 33.

Accordingly, while *Baichwal* may disclose a sustained release dosage form, it discloses a matrix dosage form which is not taught to increase the therapeutic index of oxybutynin. *Baichwal* Col. 4, line 1, for example. *Baichwal* further discloses that it releases more than about 50% of the active ingredient within the first four hours after delivery. *Baichwal* Tables 3, 6, 9, 12, 15, 18. As such, *Baichwal* teaches a dosage form that was found by Applicants to lose its sustained release benefits and to have a lower bioavailability and hence a lower therapeutic index.

Baichwal does not anticipate Applicants' osmotic dosage form as it does not teach a dosage form for increasing the therapeutic index of oxybutynin. Therefore, Claims 1, 2 and 4 are not anticipated by *Baichwal,* are patentable and are now in condition for allowance.

Claims 7-14 are rejected under 35 U.S.C. 102(b) as being anticipated by *Aberg et al.* (US Pat. No. 5,532,278). In particular, the Examiner asserts that *Aberg* teaches a method for treating urinary incontinence while avoiding and reducing adverse effects.

As discussed above, Applicants amended claims more particularly point out that their invention increases the therapeutic index of oxybutynin to concomitantly reduce side effects.

Applicants claimed dosage form contains oxybutynin or its therapeutically acceptable salts in a dosage form that increases the therapeutic index of oxybutynin. However, *Aberg* teaches reducing side effects by administering therapeutically effective amounts of (S)-oxybutynin substantially free of its R enantiomers. *Aberg* Abstract and Claim 1, for example. Applicants invention does not require use of a specific enantiomer, but allows use of the racemic mixture and delivers the mixture such that a higher therapeutic index is produced and side effects are reduced. *Aberg* does not teach a particular delivery method for increasing the therapeutic index and reducing side effects, but rather teaches delivering only the non-metabolite (S)-oxybutynin enantiomer, substantially free of its R enantiomer.

Aberg does not anticipate Applicants' osmotic dosage form as it does not teach a dosage form for increasing the therapeutic index of oxybutynin to reduce side effects without having to deliver only the beneficial enantiomer of oxybutynin. Therefore, Claims 7-14 are not anticipated by *Aberg,* are patentable and are now in condition for allowance.

For these reasons, Applicants believe that reconsideration of the rejection of claims 1, 2, 4, and 7-14 is warranted and withdrawal of the rejection is respectfully solicited.

Claim Rejections – 35 U.S.C. § 103(a) obviousness

Claims 3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being obvious over *Baichwal et al.* The Examiner asserts that through experimentation a suitable rate of release of oxybutynin could be determined. This rejection is respectfully traversed because Applicant's invention is not *prima facie* obvious from the disclosures of the cited references. In order to be *prima facie* obvious over a combination of references, the references must describe or teach each of the claim limitations and the references must themselves suggest their particular combination and a reason for that combination without reference to Applicant's application. None of the references, either taken alone or in combination, are considered to establish the *prima facie* obviousness of those claims, and the Examiner has not met the burden in properly rejecting the claims.

This rejection is respectfully traversed because there is no teaching in *Baichwal* to motivate a slower rate of release. Furthermore, there is no teaching in *Baichwal* that its matrix dosage form could be modified to any other rate of release not disclosed.

As discussed above, applicants amend their claims to particularly claim the increase in the therapeutic index of oxybutynin through the present invention that is not obtained through matrix formulations which release at least about 50% of the oxybutynin within the first four hours after administration, of which *Baichwal* is representative.

While *Baichwal* may disclose a controlled release dosage form, there is no

motivation to seek other release rates, much disclosure that its matrix design is capable of other, especially slower, release rates. As such, *Baichwal* does make Applicants' invention obvious as it does not teach a dosage form for increasing the therapeutic index of oxybutynin as claimed by Applicants and does not teach or motivate other release rates for the delivery of oxybutynin. Therefore, Claims 3, 5 and 6 are not obvious in view of *Baichwal,* are patentable and are now in condition for allowance.

Claims 7-14 are rejected under 35 U.S.C. 103(a) as being obvious over *Aberg et al* in view of *Baichwal*. The Examiner asserts that *Aberg* teaches a method for treating urinary incontinence and reducing adverse side effects and that *Baichwal* teaches a controlled release means of delivery.

This rejection is respectfully traversed because, as discussed above, *Aberg* teaches delivery of a particular enantiomer of oxybutynin to reduce side effects whereas Applicants claim a particular controlled release of oxybutynin to increase the therapeutic index of oxybutynin and reduce side effects. There is no motivation to combine Aberg and Baichwal to allow delivery of the racemic mixture of oxybutynin at a particular controlled rate to increase the therapeutic index and reduce side effects. Moreover, there is no teaching in either *Baichwal* or *Aberg* to increase the therapeutic index through controlled release.

As such, it would not have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to prepare a controlled release matrix dosage form utilizing racemic oxybutynin to increase the therapeutic index and to reduce side effects.

It appears that the Examiner is improperly attempting to pick and choose in hindsight pieces of *Aberg* and *Baichwal*, which are not taught for the purpose asserted.

For these reasons, Applicants assert that the rejection of claims 3, 5, 6 and 7-14 is not appropriate and withdrawal of the rejection is respectfully solicited. Applicants respectfully submit that Claims 3, 5, 6 and 7-14 are patentable and are in a position for allowance.

Reconsideration of the application is respectfully requested. Please direct any questions to the undersigned attorney at (650) 564-5171.

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 01-1173.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 01-1173.

Respectfully submitted,

Dated: March 11, 2002

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Version with markings to show changes made

In the Claims:

1. (Amended) A sustained release dosage form comprising oxybutynin for use in managing the plasma concentration of oxybutynin and dry mouth associated with the use of oxybutynin, wherein the sustained dosage form upon once daily administration is characterized by the sustained release of a therapeutically effective dose of oxybutynin to provide [a patient responsive to oxybutynin for managing the plasma concentration and dry mouth associated therewith] an increased therapeutic index.

2. (Amended) The sustained release dosage form according to claim 1, wherein the plasma concentration is proportional to the sustained release dose.

3. (Amended) The sustained release dosage form according to claim 1, wherein the sustained release dosage form releases up to 25 mg per hour of oxybutynin, or [oxybutynin] therapeutically acceptable oxybutynin salt thereof.

4. (Amended) The sustained release dosage form according to claim 1, wherein the sustained release dosage form comprises up to 650 mg of oxybutynin, or [oxybutynin] therapeutically acceptable oxybutynin salt thereof.

5. (Amended) A sustained release dosage form comprising oxybutynin and a pharmaceutically acceptable carrier for managing dry mouth associated with oxybutynin, wherein the sustained release dosage form upon once daily use is characterized by a sustained release therapeutically effective dose up to 25 mg per hour to [a patient responsive to oxybutynin therapy to provide a plasma concentration

proportional to the sustained release dose for managing dry mouth] provide an increased therapeutic index.

6. (Amended) Oxybutynin for use in providing a sustained release dosage form comprising oxybutynin and a pharmaceutically acceptable carrier, wherein the sustained release dosage form contains [is characterized by comprising] up to 650 mg of oxybutynin and up to 450 mg of a pharmaceutically acceptable carrier for releasing up to 25 mg per hour of oxybutynin to [an oxybutynin receptive environment] provide an increased therapeutic index.

7. (Amended) A method for managing dry-mouth in a patent administered oxybutynin, wherein the method comprises orally administering to the patient a sustained release dosage form comprising an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt thereof, that administers the oxybutynin [in] at a controlled rate over twenty-four hours [for managing dry mouth in a patient] to provide an increased therapeutic index.

8. (Amended) A method for managing dry mouth in a patient administered oxybutynin for the management of incontinence, wherein the method comprises administering a sustained-release dose of 5 mg to 30 mg of a member selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt thereof up to twenty-four hours [for managing dry mouth in the patient] to provide an increased therapeutic index.

9. (Amended) A method for relaxing bladder muscles and for managing concomitantly dry mouth in a patient administered oxybutynin hydrochloride, wherein the method comprises administering 5 mg to 30 mg of oxybutynin hydrochloride in a

sustained rate up to twenty-four hours [for producing the intended effect] to provide an increased therapeutic index.

10. (Amended) A method for decreasing the incidence of dry-mouth in a patient administered oxybutynin, wherein the method comprises orally administering to the patient a sustained-release dosage form comprising an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt thereof, that administers the oxybutynin in a controlled rate over twenty-four hours [for decreasing the incidence of dry-mouth in the patient] to provide an increased therapeutic index.

11. (Amended) A method for decreasing dry-mouth in a patient administered oxybutynin for the management of incontinence, wherein the method comprises administering a sustained-release dose of 5 mg to 30 mg of a member selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt thereof up to twenty-four hours [for decreasing dry-mouth in the patient] to increase the therapeutic index.

12. (Amended) A method for relaxing bladder muscles and for decreasing concomitantly dry-mouth in a patient administered oxybutynin hydrochloride, wherein the method comprises administering 5 mg to 30 mg of oxybutynin hydrochloride in a sustained-rate up to twenty-four hours [for producing the intended effects] to increase the therapeutic index.

13. ✓(Cancelled) The use of a sustained release dosage form in the manufacture of once daily oxybutynin therapy and the management of dry mouth associated therewith, which manufacture comprises the incorporation into a sustained release dosage form adapted for once daily admittance into an environment of use for oxybutynin therapy and concomitantly dry mouth associated therewith.

14. (Amended) [The use of oxybutynin in the] A method of manufacture of a sustained release dosage form indicated for oxybutynin therapy and for the management of dry mouth associated therewith, the manufacture comprising the step of incorporating oxybutynin into a sustained release dosage form, which when admitted daily into an environment of use releases oxybutynin [and provides management of dry mouth associated therewith] to provide an increased therapeutic index.